REMARKS

In accordance with the Examiners suggestion, Claims 2 and 5 are now independent and have been amended to include the structure of the remainder of the molecule with is identical to naturally occurring epothilones A and B. No new matter has been added.

Rejections under 35 USC §112, first paragraph

Claims 1-2, 5-6, 9-12 and 32 stand rejected under 35 USC § 112, first paragraph, because the specification allegedly does not provide a definition for "one of R^{10} and R^{11} is H, and the other is 2-Methyl-2-thiazoyl."

With regards to claims 1, 6, 9-12, 31 it is not clear to the applicants exactly what new matter the Examiner is objecting to. Only claims 2 and 5 contained the limitation "one of R^{10} and R^{11} is H, and the other is 2-Methyl-2-thiazoyl." Thus, the rejection should be withdrawn at least as to claim 1 and claims dependent thereon.

Regarding claims 2 and 5, originally presented claims 2 and 5 recited the phrase "...the remainder of the molecule is identical to naturally occurring epothilone A or B." The "remainder" includes the X group. The first paragraph of the specification provides a structure and reference to naturally occurring epothilone A and B. In response to the Examiner's objections in the Office Action of 7 September 2004, Applicants amended claims 2 and 5 to depict the naturally occurring structural variable for X. Further in accordance with the Examiner's suggestion, in the Reply of 8 July 2005, Applicants amended claims 2 and 5 to remove the structural variables for X and replace it with "$CR^{10}R^{11}$ wherein one of R^{10} and $R^{11}$is H and the other is 2-methyl-4-thiazolyl." This defines the naturally occurring structure at the X position. Now, pursuant to the Interview, the actual structure showing the naturally occurring part is shown in the actual formula; see the formula on page 1 of the disclosure. All of these versions cover the same subject matter, which is identical to the subject matter of original claims 2 and 5 and, thus, clearly has written description support.

Further, as the Examiner notes at page 2 of the Office Action, species of compounds containing the 2-methyl-4-thiazolyl are exemplified thus providing

antecedent basis and written description. Literal recitation is not necessary for adequate written description; see In re Lukach, 169 USPQ 795 (CCPA 1971); Kennecott Corp. v. Kyocera International, Inc., 5 USPQ2d 1194, 1197 (Fed. Cir. 1987); Martin v. Johnson, 172 USPQ 391 (CCPA 1972); and In re Wertheim, 191 USPQ 90, at 98 (CCPA 1976). As noted above, the original disclosure clearly encompasses compounds of the currently claimed structures, for example, the first paragraph of the specification which provides a structure and reference to naturally occurring epothilone A and B and the numerous compounds shown in the original specification. Thus, the recitation in claims 2 and 5 does not bring the claims outside the originally disclosed scope. However, in the interest of furthering prosecution Applicants have amended claims 2 and 5 to include the remainder of the structure that is identical to naturally occurring epothilone A or B, as suggested by the Examiner in the interview of 24 January 2006.

Withdrawal of the rejection is respectfully requested.

Rejections under 35 USC §103(a)

Claims 1-2, 5-6, 9-12 and 31 have been rejected under 35 USC 103(a) over CA 132:293587 and Nicolaou et al. Applicants respectfully traverse the rejection.

The rejection is based on the premise of homology. At page four of the Office Action, the Examiner incorporates the rejection rationale delineated in the office action dated March 4, 2004. At page 5 of the March 4, 2004 rejection the Examiner alleges that:

> "the difference between the prior art compound and the instantly claimed compounds are the alkyl groups at the R^{2a} and R^{2b} positions. In the instant compounds the R^{2a} and R^{2b} groups are ethyl. In the prior art compounds the R^{2a} and R^{2b} groups are methyl. The prior art compound and the instant compound are homologues of each other."

It is asserted that the claimed compounds are structurally similar to the Nicolaou et al. compound and, thus, one of ordinary skill in the art would expect the compounds to possess similar properties.

Applicants respectfully submit that, even if the assertion is true, a prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed

compounds possesses unexpectedly advantageous or superior properties. See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and MPEP 2144.09. Applicants have met the burden of proof. The declaration of Dr. Klar destroys the presumption that the similarly structured compounds would have similar properties. Compounds of the present invention possess significant and unexpected properties as evidenced by the declaration of Dr. Klar.

The declaration of Dr. Klar presents the activity of twenty-one different compounds, each of which was tested in multiple assays resulting in 62 anti-proliferative values (IC_{50} values). Thus, a direct comparison of multiple activities was made between eleven different compounds in which the R^{2a} or R^{2b} group of Applicants' formula 1 are ethyl or higher alkyl vs. ten different compounds in which the R^{2a} or R^{2b} group are methyl. Applicants have unquestionably demonstrated the structural activity relationship of the R^{2a} and R^{2b} groups. No further test data should be required. Such would be essentially redundant and would seem to serve for nothing except perhaps to unduly burden the inventor.

The Examiner asserts that the declaration cannot support the instant scope which is not commensurate with the unexpected properties of the declaration. However, a comparison of the claimed and prior art inventions to show nonobviousness only requires that prior art compounds disclosed by the reference be compared. Otherwise, for instance, it would not be possible to show nonobviousness of a selected species invention within a generic disclosure. As the Court of Appeals for the Federal Circuit has stated in In re Geiger, 2 USPQ2d 1276 (Fed. Cir. 1987), at 1279,

> " It is not required that the claimed invention be compared with subject matter that does not exist in the prior art. The Appellant is not required to create prior art...".

Furthermore, the Examiner has not provided any motivation or guidance within Nicolaou et al. to alter the structure to arrive at a genus wherein the R^{2a} or R^{2b} groups are ethyl or higher alkyl. The declaration provided by Dr. Klar clearly shows that it is profoundly advantageous to replace the 6(10)-methyl group present in naturally occurring epothilones with a higher alkyl. This 6(10)-methyl group corresponds to the

R^{2a} or R^{2b} group of Applicants' formula 1. The data are clearly representative of the significance in the difference between the methyl compounds of Nicolau and the currently claimed compounds. Thus, the presumption of similar properties, which forms the basis for the rejection, is disproven. As previously noted, the data shows that numerous representative compounds of the instant claim scope have advantageous antiproliferative properties and improved sensitivity to MDR cell lines compared to naturally occurring epothilone B and epothilone D. The declaration evidence and applicants' previous remarks thereon should, therefore, be favorably reconsidered.

Withdrawal of the rejection is respectfully requested.

The Double Patenting Rejections

A terminal disclaimer referring to this application has been filed in the 09/913,163 application. The '163 application has been noticed for patent issuance. Thus, the double patenting rejection based on the '163 application should be withdrawn. Because this application has an earlier filing date than the '163 application, filing an additional terminal disclaimer in this application serves no purpose and should not be required.

Applicants respectfully disagree with the double patenting rejection over the 10/631,011 application. The Office Action appears to treat the named partial structures of the claimed conjugates in claim 3 of the '011 application as individually named compounds that are separate or separated from the claimed conjugates. Since the mailing of the 17 October 2005 Office Action, Claim 3 of 10/631,011 has been amended and the named partial structures pointed out in the office action have since been deleted from claim 3. Furthermore, Claim 3 of said application is directed to an effector conjugate which is a chemical combination of the specifically named partial structures (one of which was pointed out in the Office Action and has since been deleted), and a structure of formula III or IV, which are covalently bound to each other to form the effector conjugate. These partial structures are claimed as the "effector element" of the claimed conjugate. See the first two lines of claim 3 of the '011 application. Nothing in the claims of the '011 application teaches or suggests the breaking up of the claimed conjugates to obtain the partial structures listed in claim 3 as separate compounds. Thus,

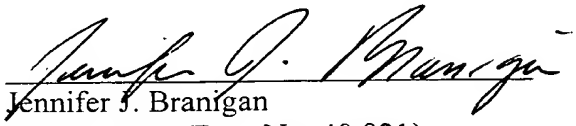
the instant claims are directed to patentably distinct subject matter and not an obvious variant of claim 3 or any other claim of the '011 application.

Similarly, the claims of US 6,610,736 require the R^8 group to be cyano or halogen. The present claims do not include compounds where R^8 is cyano or halogen. Nothing in the claims of the '736 patent teach or suggest modifying the R^8 group in any way. Thus, the current claims are not obvious variants of the claims of the '736 patent.

Withdrawal of the rejections is respectfully requested.

In view of the above remarks, it is respectfully submitted that the claims of the application are fully supported by the specification and as such are in order for allowance.

Respectfully submitted,



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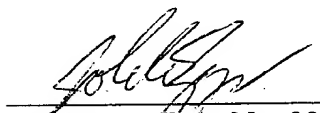

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